UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/147,912	11/03/93	WAHL	G P419498

EXAMINER: LOW, C

ART UNIT	PAPER NUMBER
1814	26

DATE MAILED: 07/14/94

18M2/0714

STEPHEN E. REITER
PRETTY, SCHROEDER, BRUEGGEMANN & CLARK
444 S. FLOWER ST., STE. 2000
LOS ANGELES, CA 90071

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

07/14/94

☒ This application has been examined ☒ Responsive to communication filed on 9 May 1994 ☒ This action is made final.

A shortened statutory period for response to this action is set to expire three (3) month(s), 0 days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 25, 26, 28, 42-46, and 48 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 25, 26, 28, 42-46, and 48 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

PTOL-326 (Rev. 2/93)

The text of those sections of Title 35, U. S. Code not included in this action can be found in a prior Office Action.

The corrections to the specification and the amendment to claims 25, 26, 28, 42-44, and 48 in the response filed 9 May 1994 are noted. In view of the amendments, the following grounds of objection and rejection are or remain applicable to pending claims 25, 26, 28, 42-46, and 48.

The specification remains objected to under 35 U.S.C. 112, first paragraph, as failing to provide a reasonable written description, enablement and best mode for practicing the claimed invention; and, claims 25, 26, 28, 42-46, and 48 remain rejected under 35 U.S.C. 112, first paragraph, for the reasons set forth in the objection to the specification, both for the reasons indicated in the prior Office Action.

The comments (pages 6-9) in the response filed 9 May 1994 are noted, however, as admitted in said present response, the first site (i.e., the initial site) is not targeted. Where that first site is not targeted as admitted in the present response, there is no way that integration can be precisely targeted as the location of the first site is not targeted as pointed out in the prior Office Action which indicated the specification does not disclose how the initial FRT site is precisely inserted (i.e., targeted) to the specific DNA. Note that precise genomic targeting requires not only the DNA to be inserted but that the location to which it is to be inserted also be precisely identified and/or not targeted as admitted in the present response. Absent such teaching, it cannot be said that the DNA to be targeted to the first preexisting site is precisely targeted to some known location on a DNA when that location on the DNA is unspecified. Since the integrating DNA recombines with the FRT site, but where the location of the preexisting site is unspecified, there is no precisely targeting the integrating DNA to any specified location in the genome; i.e., the problem of inability to control the location of integration of the initial FRT site remains as the specification does not disclose how the initial FRT is integrated at predetermined sites on a chromosome. See present specification page 12, paragraph bridging pages 12-13. How does the first FLP site get specifically and precisely integrated into the genome? Note that the first full paragraph of present specification page 12 dose not detail how this is done and is subject to the inability to control the site of integration referred to at present specification page 1. Thus, where the initial site is not targeted, the present claims indicating precise targeting is not described, enabled, nor is a best

mode disclosed for precisely targeting even the first site. Note that the claims do not indicate that the first site is not precisely targeted; and therefore, such precise targeting refers to all sites. The discussion at response pages 7-9 are not convincing as to any of the above for the above indicated reasons.

Claims 25, 26, 28, 42-46, and 48 remain rejected under 35 U.S.C. 112, first paragraph, as the disclosure is not enabled for precisely targeting the DNA to a predetermined site of that integration, i.e., the first FLP recombination target site is not precisely predetermined by its own location in the genome of the cell as indicated in the prior Office Action.

The comments (pages 9-11) in the response filed 9 May 1994 are noted but are not persuasive because as indicated in the prior Office Action, the present specification contains no disclosure of how the first DNA is targeted to a precisely predetermined site of that integration, i.e., the first FLP recombination target site is not precisely predetermined by its own location in the genome of the cell as indicated in the prior Office Action and as admitted in the present response. Thus, here, where the location of the first DNA is not targeted, the location of any additional DNA is also not specifically targeted to a specific predetermined site that has been predetermined for the first site prior to its integration into the genome. Thus, the comments in the response at pages 9-11 are not convincing.

Claims 25, 26, 28, 42-46, and 48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 25 is indefinite as lines 1-2 indicate recitation of precisely targeting a DNA but do not indicate that it is only the second DNA that is targeted. As presently recited, the claim also calls for precise targeting of the first DNA as the "a nucleic acid" refers to both the first and second DNA fragments. Claim 26 is indefinite as it calls for excision of the DNA however, the presence of the same enzyme in claim 25 effects an insertion recombination. Note that it is expected that the same steps effect the same result. What is the result of treating the host cell DNA with the enzyme? Is it recombination by insertion or excision? The same step (putting the DNA into the presence of the enzyme to effect catalytic recombination cannot by thermodynamics and entropy run forwards and backwards under the same conditions but for dynamic equilibrium (i.e., substrates of two DNAs are formed into one product (insertion) as

fast as the reverse reaction is carried out (i.e., substrate of one DNA is excised to form product (two DNAs))). Note that for claims 25 and 26, the conditions (i.e., time, temperature, concentration, pH, etc. under which the enzyme is used are not *per se* indicated as demonstrably different in the claims. In claim 28, the presence of the third FRT is noted, but said claim is also indefinite as to whether or not the first and third sites, first and second sites, as well as the second and third sites recombine in the presence of the recombinase. The claims indicate no specificity for interaction with only selected sites and, thus, where the first and second sites have recombined, there is no indicated specificity to for only recombination with sites 1 and 3 but not 2 and 3. Thus, claim 28 is indefinite. Claim 42 as well as claim 44 are indefinite as to the site specificity (see the reasons above as to claim 25 with regard to the "precisely targeting"). In claims 43 and 44, where the first site is not targeted (as admitted in the response) the claim is not clear as to how that site is precisely targeted to a gene of interest. In claims 42 and 43, it is also not clear as to the metes and bounds of a partial coding sequence as to whether it refers to the DNA of the '5-end, the 3'-end, the middle or both ends, or whether it refers to DNA wherein every other codon has been removed or contains substitutions. Claim 43 is indefinite as to "FRT(s)" and "is/are" as it is not clear whether the claim recitation of "FRT(s)" refers to a single or a multiplicity of "FRT" sites. Claim 48 is indefinite as when the first DNA is integrated into the genome, it is no longer present as a first DNA, and thus, it is not clear how a second DNA recombines with a first DNA that no longer exists as a first DNA. Claims 42 and 48 are also indefinite as the reference to "a first gene of interest" infers a "second gene of interest" but which is not indicated in claim 42 or 48. In the pending claims it is also unclear as to whether or not the cells contain any naturally occurring FRT sites the unknown location of which would affect the recited "precise targeting". What defines "a partial coding sequence" (claim 44)? What functional portions are referred to in the claims and how big is a partial coding sequence in nucleotide bases (is it one base or $5X10^6$ bases)?

The comments (pages 11-12) in the response filed 9 May 1994 are noted but are not persuasive for the above indicated reasons which amended claims necessitate the above rejection. As to the naturally occurring FRT sites the unknown location of which would affect the recited "precise targeting" the response at page 12 refers to DNA for FRT sites from *S. cerevisiae*, however, the instant claims do not so indicate.

Claims 25 and 28 remain rejected under 35 U.S.C. 102 (b) as anticipated by or, in the alternative, under 35 U.S.C. 103 as obvious over Golic *et al.* for the reasons indicated in the prior Office Action.

The comments (pages 13-15) in the response filed 9 May 1994 are noted but are not persuasive. As to the assertion of insects as opposed to mammalian systems, it is not persuasive as the reference indicates (page 499) mammalian systems as being known. It is indicated that FRT bearing plasmids can be directed to the site of an FRT already resident in the genome for germline transformation which would have resulted in a process for producing the host organism as well as integration into the genome. The step of mating the flies (page 500), is a step of introducing into the cells (which are indicated as already having an FRT site (page 499) in the *w* gene) that are the male or female gametes into the other *D. melanogaster* gamete wherein Golic *et al.* disclose that FLP catalyzed recombination between FRTs in the germline and the soma. In the alternative, it would have been obvious from the disclosure which indicates that "we expect the it will work in other organisms as well" to expect the process to function in other organisms which are higher eukaryotes (page 499, left column) where mammalian cells (page 499 right column) are known higher eukaryotic cells.

As to the assertion of independent statements in the Golic *et al.* reference, they are not independent but are part of one and the same reference as required of 35 U.S.C. 102. Thus, the comments at page 13 are not convincing. It is also noted and not well taken that the response alleges that the comments are taken out of context. They are not taken out of context and the reference has been considered in entirety. Is it noted that response page 14 cited *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.* as to picking and choosing. Such is not the case here as all of the reference is considered and citation of what the reference discloses and suggests is not picking and choosing but is pointing out of the most relevant parts of the reference to applicant. Therefore, citation of the above decision is not persuasive.

At the bottom of response page 14, the discussion refers to yeast and *Drosophila* and the reasons the Golic *et al.* reference used same. These comments are not persuasive as the DNA in the disclosed systems were known to so recombine and the reference discloses that the authors expected it to work in other organisms wherein page 499 indicates mammalian systems. Thus, applicant's comments are not persuasive as the page 507 discussion by Golic *et al.* clearly indicates expectation (i.e., it anticipates that it would work, and therefore is

anticipatory) in teaching that "we expect that it will work in other organisms as well" and thus, it is anticipatory to expect the process to function in other organisms which are higher eukaryotes (page 499, left column) where mammalian cells (page 499 right column) are known higher eukaryotic cells which makes the comments in present response erroneous.

It is applicant's response that would allege the independence of statements in a reference and such allegation is not convincing because the reference indicates use of eukaryotic cells and expects it to work in other systems and it is clearly indicated and anticipatory that where the reference indicates "mammalian systems" that it refers to mammalian systems. It is not something else and where applicant alleges no indication of other organisms (response page 15) are disclosed in the reference, that allegation is not persuasive because the reference does indicate mammalian systems (see at least page 499) as clearly had been pointed out in the prior Office Action.

Claims 25, 26, 28, 42-46, and 48 remain rejected under 35 U.S.C. 103 as being unpatentable over Sauer (U.S. '317) taken with Golic *et al.* as indicated in the prior Office Actions of this and the parent application.

The comments (page 15-18) in the response filed 9 May 1994 are noted but are not persuasive. In the paragraph bridging pages 15-16, the response comments that certain features distinguish the claims. This is not convincing because these features are not *per se* in the claims. Therefore, the comments are not convincing - note, for example, that there is no mention in the claim *per se* of yeast or even of *S. cerevisiae*.

The commentary at page 16 as to the Sauer reference is noted but not convincing as Sauer teaches site specific recombination of mammalian cells (col 14+) using plasmids with the DNA coding for the *cre* and *lox* (cols 1, 6-7). Here, applicant's comments assert the reference does not disclose chromosomally integrated DNA, however, said assertion fails to consider that the rejection is under 35 U.S.C. 103 wherein as to the discussion of the Sauer reference, at page 14, it is noted that the response discusses P1, *Cre* and *lox*, however, the comments are unconvincing as Golic *et al.* disclose site specific recombination in *D. melanogaster* with DNA coding for FLP and FRT (see at least pages 499 and 507) where it is indicated that FRT bearing plasmids can be directed to the site of an FRT already resident in the genome suggesting its use for germline transformation which would have resulted in a

transgenic animal and further indicate that "we expect the it will work in other organisms as well" which would have motivated one of ordinary skill in the art to use other cells such as those cells and teachings in the Sauer patent which discloses at cols 14+, site specific recombination in mammalian cells (mouse) where the combination of the Sauer and Golic *et al.* references would have resulted in a method for site specific recombination that featured chromosomal integration of the DNA as to have obtained a transgenic fly, that DNA is integrated into the genome and given the indications of mammalian systems by Golic *et al.* it would have been for the reasons indicated in the stated ground of rejection obvious for one of ordinary skill in the art to have at least used the mammalian system disclosed in the Sauer patent.

It is also noted that page 16 of the response argues efficiency, however, such argument is not commensurate in scope to the present amended claims and wherein the combined cited references disclose collectively to one of ordinary skill in the art that the yeast FLP/FRT works and is expected to work in other systems/organisms wherein Sauer discloses that one such system using analogous constructs to the yeast FLP/FRT functions in the manner of the present claims. These are the same sites and are disclosed in the references as having been obtained from yeast. Thus, here in view of the cited combined references which teach the same sites and recombinase as put forth in the claims, it is expected that the properties are the same, i.e., the efficiency is the same and in any event, in view of the fact that applicant's response admits of integration of the first FRT site as not targeted, applicant's comments on efficiency or of precise targeting are simply not persuasive. Thus, the comments of efficiency as to Sauer alone are not persuasive.

At the bottom of page 16, the response of 9 May 1994 discusses Golic *et al.* These comments are not persuasive as to this reference for the reasons set forth in the stated ground of rejection as well as discussed above and as indicated in the prior Office Actions. Applicant argues no precise targeting (note applicant's own admission in the response that the initial site is not targeted), but this is not convincing as the same yeast FRT sites and recombinase are used. It is expected to have the same properties. Moreover, in combination with Sauer, Golic *et al.* disclose site specific recombination in *D. melanogaster* with DNA coding for FLP and FRT (see at least pages 499 and 507) where it is indicated that FRT bearing plasmids can be directed to the site of an FRT already resident in the genome suggesting its use for germline transformation which would have resulted in a transgenic animal and further indicate that "we

expect that it will work in other organisms as well" which would have motivated one of ordinary skill in the art to combine the teachings of Sauer which discloses at cols 14+, site specific recombination in mammalian cells (mouse) where the combination of the Sauer and Golic *et al.* references would have resulted in a method for site specific recombination in mammalian cells or in transgenic animals. Moreover, where both Sauer and Golic *et al.* teach that the DNA for the FLP and FRT are from yeast, Sauer teaches at col 5, mating the yeast of opposite mating types which contain the plasmids with the DNA for the FLP and FRT which is a step of introducing the cells produced by the step (i) and (ii) of claim 28 into the subject where the subject is another yeast cell and where Golic *et al.* disclose mating the flies (page 500), it is a step of introducing the cells which are the male or female gametes into the subject where the subject is the other *D. melanogaster* gamete which after fertilization becomes a transgenic fruit fly.

At page 17, the response discusses rationale and alleges that the references teach away from the claimed invention. These comments are not persuasive because there is and have been clearly stated reasons for combining the references based upon teachings in the reference wherein where Sauer teaches site specific recombination of mammalian cells (col 14+) using plasmids with the DNA coding for the *cre* and *lox* (cols 1, 6-7). Where Sauer does not explicitly disclose the use of DNA coding for FLP and FRT, it would have been obvious to one of ordinary skill in the art to use DNA coding for FLP and FRT in vectors for transforming *D. melanogaster* because Golic *et al.* disclose site specific recombination in *D. melanogaster* with DNA coding for FLP and FRT (see at least pages 499 and 507) where it is indicated that FRT bearing plasmids can be directed to the site of an FRT already resident in the genome suggesting its use for germline transformation which would have resulted in a transgenic animal and further indicate that "we expect that it will work in other organisms as well" which would have motivated one of ordinary skill in the art to combine the teachings of Sauer which discloses at cols 14+, site specific recombination in mammalian cells (mouse) where the combination of the Sauer and Golic *et al.* references would have resulted in a method for site specific recombination in mammalian cells or in transgenic animals. Moreover, where both Sauer and Golic *et al.* teach that the DNA for the FLP and FRT are from yeast, Sauer teaches at col 5, mating the yeast of opposite mating types which contain the plasmids with the DNA for the FLP and FRT which is a step of introducing the cells produced by the step (i) and (ii) of claim 28 into the subject where the subject is another yeast cell and where Golic *et al.* disclose mating the flies (page 500), it is a step of introducing the cells

which are the male or female gametes into the subject where the subject is the other *D. melanogaster* gamete which after fertilization becomes a transgenic fruit fly. Thus, the comments as to no motivation are not convincing.

The response indicates that page 499 of Golic *et al.* teach away from the invention by using *D. melanogaster*, however, as applicant's response, previously alleges, here it is applicant's response that argues the contents of that paragraph incorrectly. The paragraph does not state that mammalian cells or systems do not work but only that a choice of materials to use was made. This does not mean that other systems do not work, in fact the reference when taken in entirety says exactly the opposite, that the authors expected it to work in other organisms and that other organisms included mammalian systems wherein Golic *et al.* indicate at page 499 (right column) that a protein evolved to function in a eukaryotic cell (i.e., the yeast FLP, FRT, and recombinase wherein yeast is a eukaryotic cell) would be expected to work in a eukaryotic cell such as that of a fruit fly as well as in a mammalian system as a mammalian system is composed of eukaryotic cells. It is also noted that Golic *et al.* indicate *cre* and *lox*, however, these do not teach away from the present invention, rather they indicate analogous systems and analogous systems that function to perform site specific recombination is not a teaching away from the invention as analogous systems that work in the same manner as the yeast FRT/FLP.recombinase lend support to the Golic *et al.* disclosure as supporting the fact that the authors expect it to work.

It is also noted that the response argues that the complexity of the mammalian genome makes the *Drosophila* genome elementary is incorrect, erroneous, and plain wrong as were the genome so elementary, then applicant should be able to make an intact functioning fruit fly from the elements carbon, hydrogen, oxygen, nitrogen and the appropriate trace elements by traditional chemical synthesis. Here, were man has not even succeeded it making an *E. coli* by such a method, it is not elementary or simple but an exceedingly complex task. Thus, such argument in the response simply flies in the face of fact and of logical deduction.

Claims 25, 26 and 28 remain rejected under 35 U.S.C. 103 as being unpatentable over Sauer (U.S. '317) taken with Golic *et al.*. as applied to claims 25, 26, 28, 42-46, and 48 above, and further in view of Palmiter *et al.* as directed to the "mammalian host cell" as being in a transgenic animal for the reasons indicated in the Office Actions of this and the parent application.

The comments (page 18-19) in the response 9 May 1994 are noted but are unpersuasive for all of the above indicated reasons as to Sauer and Golic *et al.* which are applied herein. It is noted that the response indicates (page 18) that the Palmiter *et al.* reference does not cure the combination of Sauer and Golic *et al.*, note however, that the comments as to Sauer and Golic *et al* in applicant's present response are not convincing, thus commentary as to Palmiter *et al.* not curing Sauer and Golic *et al.* are not convincing and the references of Sauer and Golic *et al.* when combined do in fact show that DNA from yeast a singly celled eukaryote does recombine with that of a multicellular eukaryotic organism wherein the Golic *et al.* reference expects it to work with other systems where in the Golic *et al.* reference indicates mammalian systems and where Sauer and Golic *et al.* are applied as indicated above and where Golic *et al.* indicates expectation of success as indicated above, one of ordinary skill in the art would have found it obvious to combine the teachings in the Palmiter *et al.* reference which discloses introduction of the transforming DNA into totipotent teratocarcinoma cells or embryonic stem cells which can be introduced into the developing embryo by aggregation of the cells. Here, where Sauer taken with Golic *et al.* disclose the plasmids with the FLP and FRT DNA for site specific recombination, it would have been obvious to one of ordinary skill in the art given that Golic *et al.* indicate that "we expect that it will work in other organisms as well", to modify the process by using totipotent teratocarcinoma cells or embryonic stem cells as disclosed by Palmiter *et al.* which are later aggregated with the developing mouse embryo. Thus, the comments in the response as to this ground of rejection are not persuasive.

No claim is allowed.

Applicant's amendment necessitated the new grounds of rejection. Accordingly, THIS ACTION IS MADE FINAL. See MPEP 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 CFR 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE

STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

An inquiry concerning this communication should be directed to Christopher Low at telephone number (703) 308-0196.

CSFL
12 July 1994

Christopher S.F. Low

CHRISTOPHER S. F. LOW
PRIMARY EXAMINER
GROUP 1800